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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/761,169 | 01/20/2004 | Ali O. Gure | L0461.70073US01 | 3734 |

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| EXAMINER | |
|---|---|
| REDDIG, PETER J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/761,169 | GURE ET AL. | |
| | Examiner | Art Unit | |
| | Peter J. Reddig | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *6,9,10 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,11,12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## *DETAILED ACTION*

1. The Amendment filed October 30, 2006 in response to the Office Action of June 27, 2006 is acknowledged and has been entered.

2. Claims 1-14 are pending.

3. Claims 6, 9, 10, and 13 remain withdrawn from consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-5, 7, 8, 11, 12, and 14 are currently under consideration.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following rejections are being maintained:

### Claim Rejections - 35 USC § 112

7. Claims 1-5, 7, 8, 11, 12, and 14 remain rejected under 35 U.S.C. 112, first paragraph. In response to the rejection of claims 1-5, 7, 8, 11, 12, and 14 under 35 U.S.C. 112, first paragraph in section 5, pages 5-9, of the Office Action of June 27, 2006, Applicant argues that Vural et al. (Cancer 2005; 103:2575-2583), in a post filing publication, teaches that SOX1 and ZIC2 antibodies in SCLC correlate with better cancer prognosis and points to the paragraph bridging pages 2577-2578.

The argument has been considered, but has not been found persuasive because a review of the paragraph bridging pages 2577-2578 reveals that the paragraph in fact states that "a trend towards better response to initial therapy was observed in all of the seropositive patients compared with the 74% response rate in seronegative patients" with a significant difference being observed only for groups with either SOX1 and/or ZIC2 antibodies.

Applicant argues that, in particular, SCLC patients with one or both of SOX1 and ZIC2 antibodies have limited stage disease and significantly better response to therapy.

The argument has been considered, but has not been found persuasive because the claims are not limited to SCLC patients with one or both of SOX1 and ZIC2 antibodies and have limited stage disease and significantly better response to therapy.

Applicant further argues that Vural et al. supports determination of prognosis based on the antibodies and points specifically to Table 3, Figure 3, and Figure 4 to show the correlation of the presence of the antibodies and time to disease progression.

The argument has been considered, but has not been found persuasive because Figure 3 is drawn to only high titer anti-SOX1 antibody patients and the claims are not limited to high titer anti-SOX1 antibody patients. Furthermore, the data in Table 3, of which Figures 3 and 4 appear to be graphical representations, teaches that there is substantial overlap in median time to progression for seropositive SOX1 and/or ZIC2 groups compared to seronegative groups with high variability (see the overlapping ranges in the 95% CI column of Table 3). Thus, the meaning of the data in Table 3 and Figures 3 and 4 cannot be determined as to whether or not Vural et al. supports the determination of prognosis based on the antibodies to SOX1 and/or ZIC2.

Further, it is noted that the study presented in Vural et al. is a retrospective study, precisely the type of study that Tockman et al. specifically teach is not sufficient to validate prognostic markers. Finally, although Vural et al. concludes that these observations indicate that seropositivity to SOX1 Group B and ZIC2 is associated with a better clinical outcome, this is in

reference to better responses to therapy (see p. 2581, 2nd para, left column) which is quite different than prognosticating disease progression.

In response to Examiner's arguments that the specification does not provide guidance for correlating levels of SOX1 or ZIC2 antibodies with patient prognosis, Applicant argues that Examiner's description shows that the skilled person routinely performs validation studies, and thus any experimentation required for validation cannot be undue experimentation.

The argument has been considered, but has not been found persuasive because although it is known in the art how to validate a biomarker for successful clinical application in the absence of validating the marker against acknowledged disease end points, establishing quantitative criteria for marker presence/absence, and confirming the markers predictive value in prospective population trials a marker is not validated. The specification and art of record do not teach these aspects of marker validation for anti-SOX1 and ZIC2 antibodies and validation is not routine for one of ordinary skill in the art, thus undue experimentation would be required to practice the broadly claimed invention.

Applicant argues that the titer of antibodies is indicative of certain clinical parameters such as disease state, etc. In particular, applicant points to p.2581, left column, first full paragraph.

The argument has been considered, but has not been found persuasive because the teachings of the specification and Vural et al. do not support the using the presence or levels of antibodies to SOX1 and ZIC2 as an indication of disease regression or progression. In particular, Vural et al. teach that antibodies to SOX-1 and ZIC-2 remained stable over the periods of treatment tested. During this period in which the anti- SOX-1 and ZIC-2 antibodies remained

present and stable several of the patients had complete remissions, partial remissions, or progressive disease. Two patients with complete remission (CR), patients 8 and 71, and two patients with partial remission (PR), patients 19 and 63, had the same level of anti-SOX-1 antibody as a patient with progressive disease, patient 4, see p. 2579, **Antibody Titers during the Course of Disease** and Fig. 5.

Thus, the presence or level of antibodies to SOX-1 or ZIC2 did not indicate progression or regression of SCLC. Although Vural et al. teach that SOX1 and/or ZIC2 seroreactivity was found to be associated with better responses to therapy, longer survival, and improved time to disease progression this is not commensurate in scope with using the presence or levels of antibodies to SOX1 and ZIC2 as an indication of disease regression or progression. Thus, without data demonstrating that the presence or level of antibodies to SOX1 and ZIC2 can be used as an indication of disease regression or progression undue experimentation would be required to make and use the broadly claimed invention.

8. In response to the rejection of claims 1-5, 7, 8, 11, and 12 under 35 U.S.C. 112, first paragraph in section 6, pages 9-12, of the Office Action of June 27, 2006, Applicant argues that the experimentation required to practice the claimed invention in any cancer is routine because all of the methods needed to practice the invention are well known to the skilled person, and are described further in the specification, including in the working examples. Applicant argues that the critical piece of information, i.e., that presence of these antibodies indicates the presence of cancer and/or provides an indication of prognosis, progression, etc., is provided by Applicant in the specification.

Applicant's arguments have been carefully considered, but have not been found persuasive because the teachings of the specification that indicated that the presence of antibodies to ZIC2 and SOX1 is important as an indication of regression, progression, or onset of SCLC is not commensurate in scope with the claims which are drawn to any cancer, not just SCLC. Thus, the critical information required would be to demonstrate the importance of determining the presence or level of antibodies to ZIC2 and SOX1 as an indication of regression, progression, or onset in other cancer types for the reasons of record.

Applicant further argues that Example 3 provides an example of expression of these gene products in cancers other than SCLC, demonstrating expression of ZIC2 in a variety of cancer cell lines and tumor samples (cell lines: non-small cell lung tumor and melanoma; tumor tissues: melanoma, colon cancer, breast cancer, head and neck cancer, lung cancer, transitional cancer, leiomyosarcoma and synovial sarcoma). Applicant argues that given the results with SOX and ZIC2 gene expression in SCLC cells and tumor samples and antibodies to these proteins in cancer sera of SCLC patients, the person of skill in the art is provided with a clear direction and an expectation of success to determine the presence of antibodies to these proteins in sera of other cancer patients.

Applicant's arguments have been carefully considered, but have not been found persuasive because Example 3 measures the expression of ZIC2 mRNA in cell lines and tumors and the presence of mRNA is not indicative of the presence of antibodies to the protein encoded by the mRNA. As an illustration of this, the specification teaches that ZIC2 mRNA was expressed in normal brain and testis tissues and SOX2 mRNA could be detected in normal brain,

testis, prostate, small intestine, and colon of tissues, but only one of 16 of the normal sera showed weak reactivity for SOX2 antibodies, see Examples 3-5.

Applicant further argues that the experimentation required to practice this aspect of the invention can be done rapidly and routinely using standard immunoassays of sera, including stored sera samples, and including automated/high-throughput methods. Applicant argues that exemplary methods were described in the specification and in the working examples and, thus, there is a significant amount of guidance provided in the specification.

Although applicant suggests that it was within the skill of the art and routine to screen other cancers for the presence of antibodies to ZIC2 and SOX1, the screening assays taught and exemplified in the specification do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir. 2004) that screening assays are not sufficient to enable an invention since they are merely a wish or plan for obtaining the claimed chemical invention. Applicant is reminded that 35 USC 112 first paragraph does not require that the specification teach how to "screen" for the claimed invention, rather 35 USC 112 first paragraph requires that requires that the specification teach how to make the claimed invention. It is clear from Applicant's suggestion that the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, that is the ability to determine if the presence of antibodies to ZIC2 and SOX1 is important as an indication of regression, progression, or onset of any cancer other than SCLC. Since the making of the broadly claimed invention is not enabled, one would not know how to use the broadly claimed invention.

Applicant argues that the experimentation required to practice this aspect of the invention can be conducted by a competent technician (i.e., having a level of skill equal to or less than the person of ordinary skill in the art). Applicant argues that exercise of routine experimentation to practice the invention is not sufficient for an enablement rejection. Applicant argues that the application of the claimed methods to other cancers might require some amount of experimentation, but such experimentation is not undue if it is the sort practiced in the art. Applicant argues that this is analogous to the situation in Wands, in which monoclonal antibody-secreting hybridomas were screened, see In re Wands, 858 F.2d 731(Fed. Cir. 1988). Applicant argues that two of the factors used by the court to decide in favor of enablement in the Wands case are equally applicable here: all of the methods needed to practice the claimed invention were known, and there was a high level of skill in the art. Applicant argues that sufficient guidance was provided to guide the skilled artisan to the use of the claimed methods in cancers other than SCLC.

Applicant's arguments have been carefully considered, but have not been found persuasive because given the information in the art as previously set forth, it cannot be predicted that the claimed invention would be effective for any other cancer type for the reasons previously set forth and further for those reasons no one of skill would believe that it was more likely than not that the invention would function as broadly claimed.

Applicant's arguments have not been found persuasive and the rejections are maintained.

9. All other objections and rejections recited in the Office Action of June 27, 2006 are withdrawn.

10. No claims are allowed.

11. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

12. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR